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| 10/757,827 | 01/15/2004 | Michael R. Rosen | 13533/48003 | 5518 |

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| EXAMINER | |
|---|---|
| SINGH, ANOOP KUMAR | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/757,827 | ROSEN ET AL. | |
| | Examiner | Art Unit | |
| | ANOOP SINGH | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *20,49,51,57,59 and 65-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,49,51,57,59 and 65-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/21/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/21/2010 has been entered.

Applicants' amendment to the claims filed July 21, 2010 has been received and entered. Applicants have amended claims 49, 51, 57, 59, 66-67, while claims 1-19, 21-48, 50, 52-56, 58 and 60-64 have been canceled. Applicants have also added claims 70-71 that are generally directed to elected invention. Claims 20, 49, 51, 57, 59, 65-70 and 71 are pending in this application.

***Election/Restrictions***

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group was found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49, 51, 57, 59, 65-70 and 71 are under consideration in the instant application.

***Withdrawn-Claim Rejections - 35 USC § 103***

Claims 20, 49, 51, 57, 59, 65-68 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002), and Qu et al (Circulation res. 2001, 89:e9, IDS). Applicants' argument that there is no motivation to modify the composition of Lee to genetically modify the MSC of Lee with a nucleic acid encoding HCN is persuasive in part. Therefore, rejection of claims 20, 49, 51, 57, 59, 65-68 is

hereby withdrawn in view of new rejection addressing the deficiencies. The new rejections over the prior art of record are set forth below:

***New-Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20, 49, 51, 57, 59, 65-70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosen et al (US patent application no 20020187948, dated 12/12/2002, 06/06/2001, IDS) or Rosen et al (WO 02/098286 , dated 12/12/2001, IDS), Lee et al (Molecular Therapy, 2001, 857–866, IDS) and Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005, IDS).

The applied reference has a common Inventor Rosen, Robinson and Cohen with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that method claims require one active method step comprising introducing the composition of the invention comprising genetically modified mesenchymal stem cell (MSC) to the heart or contacting human cardio myocyte with the composition of the invention.

With respect to claims 20 and 65, Rosen et al teach a composition comprising a human myocyte incorporated with a nucleic acid which encodes a hyperpolarization activated, cyclic nucleotide gated 2 (HCN2) ion channel in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject (see claim 1 and para. 51 and 52).

Regarding claims 49, 51, 57, 59 and 66, Rosen et al teach a method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject, wherein the cell is a cardiac myocyte, cardiac condition is a cardiac rhythm disorder and the compound comprises a nucleic acid which encodes an HCN2 channel (see claims 1-7 and 11 of '948). Rosen et al further teach a method of inducing a current in the heart in a subject which comprises contacting a cell of the heart of a subject with a compound in a sufficient amount to induce a current in the cell of the heart of a subject, thereby inducing a current in the cell of the heart of the subject. Rosen further teaches a method of increasing the heart rate in a subject which comprises contacting a cell of the heart of a subject with a compound in an amount sufficient to decrease the time constant of activation and deactivation of the cell of the heart, thereby increasing the heart rate in the subject (see claims 17 and 19). It is noted that the term "cardiac cell of a heart" means a cell derived from a heart either isolated or in culture and "a cardiac myocyte" means a myocyte derived from muscle or conductive tissue of a heart, either isolated or in culture and capable of initiating a current (see para. 51 and 52 of the specification). Therefore, the term contacting a cell of heart with HCN2 is interpreted as cell from heart that is isolated, cultured and contacted with HCN2. It is further disclosed that the step of contacting is selected from the group consisting of topical application co culturing the cell with the nucleic acid (see claim 17). With respect to claims 70-71, Rosen et al teach HCN2 encoding nucleic acid is operably linked to a promoter (see para. 68).

While Rosen et al teach a composition and method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, but differ from claimed invention by not disclosing contacting genetically modified MSC.

Lee et al teach *ex vivo* culture and expansion capabilities and multi potential nature of hMSCs to make hMSCs an attractive cellular vehicle for gene delivery applications. Lee et al

show that genetically transduced MSCs expanded in culture and maintain the stem cell phenotype and stable transgene expression for over 6 months (see page 858, col. 1, para. 1). Wang et al provided guidance with respect to administration of MSC in the heart shows growth potential in a myocardial environment and indicated the formation of gap junctions (see abstract and Figure 6).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Rosen et al., Lee et al. and Wang. to modify the composition and method of Rosen et al by substituting the cardiac myocyte as gene delivery vehicle with functionally equivalent MSC as disclosed by Lee as a matter of design choice, in the composition and method for increasing the expression of ion channel (HCN2) intended for inducing pacemaker current, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. Said design choice amounting to combining prior art elements according to known methods to yield predictable results. One of ordinary skill in the art would reasonably conclude that the composition would implicitly form gap junction when directly administered to the heart of a subject particularly in view of teaching of Wang (supra). Therefore, given that MSC were available for use to express gene of interest and were routinely used as gene delivery vehicle as per the teachings of Lee, it would have obvious for one of ordinary skill in the art to modify the composition of Rosen to produce transformed MSC cells as disclosed in the instant application. One who would practice the invention would have reasonable expectation of successfully practicing the composition comprising mesenchymal stem cell incorporated with HCN2 because the art had already shown that HCN2 and other ion channel isoform could be expressed in mammalian cell as in Rosen. One of skill in the art would have had a reasonable expectation of success in combining the teachings of Rosen with those of Lee and Wang because genetically modifying mesenchymal stem cells with HCN2 would have provided a stable expression of HCN2 for longer duration and would have also formed gap junction upon administration to the heart. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

It should be noted that the *KSR* case forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obviousness See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007)

(citing *KSR*, 82 USPQ2d at 1396) (available at http: www.
Uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Claims 20, 49, 51, 57, 59, 65-70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feld et al (US patent no 7294333, dated 11/13/2007, filed on 10/20/2000), Lee et al (Molecular Therapy, 2001, 857-866, IDS, hereafter Lee 1), Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002, art of record, hereafter Lee 2), and Qu et al (Circulation res. 2001, 89:e8-14, IDS).

With respect to claim 20, and 65, Feld et al teach allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel. Regarding claims 49, 51, 57, 59 and 66, Feld et al teach a method of modifying the electrophysiological function of a heart of an individual and treating atrial fibrillation or ventricular tachycardia, the method comprising: (a) providing allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel; and (b) implanting said allogeneic or autogeneic fibroblasts into the heart of the individual, such that each implanted cell of said allogeneic or autogeneic fibroblast forms: (i) gap junctions with at least one cell of the heart; and (ii) a functional ion channel; thereby modifying the electrophysiological function of the heart and treating atrial fibrillation or ventricular tachycardia. It is further disclosed that each implanted cell of said allogeneic or autogeneic fibroblasts forms said functional ion channel following induction, wherein inward-rectifier potassium ion channel is Kir2.1 (see claims 1-3 of '333). It is further disclosed that cells are implanted in the heart by injection (see col. 17, line 14). Feld et al contemplated other cell types can be utilized to accomplish the cells posses functional gap junctions and functional ion channels including fibroblasts, skeletal myoblasts that are autologous, allogenic, or xenogenic origin (see col. 14, lines 32-36). Feld et al further disclose that the cells transplanted generate specific structural and function interactions with the cardiomyocytes via the gap junction which can be either inherent to the transplanted cells or the product of over expressed exogenes (see col. 14, lines 36-40). Regarding claims 70-71, it is

disclosed that the nucleic acid construct includes at least one promoter sequence for driving the transcription of the first and second polynucleotide regions (see col. 4, lines 45-57). While Feld et al teach a composition and method comprising a) providing allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel; and (b) implanting said allogeneic or autogeneic fibroblasts into the heart of the individual, such that each implanted cell of said allogeneic or autogeneic fibroblast forms: (i) gap junctions with at least one cell of the heart; and (ii) a functional ion channel, but differ from claimed invention by not disclosing cells and ion channel being MSC and HCN2 respectively.

Lee et al (1) provide motivation to use MSC as gene delivery vehicle for treating various conditions. Lee et al teach an ex vivo culture and expansion capabilities and multi potential nature of hMSCs to make hMSCs an attractive cellular vehicle for gene delivery applications. Lee et al show genetically transduced MSCs expanded in culture and maintain the stem cell phenotype and stable transgene expression for over 6 months (see page 858, col. 1, para. 1), but differ from claimed invention by not disclosing injecting MSC to heart or cardiac cell.

Lee et al (2) teach a composition comprising a recombinant mammalian cell that is genetically engineered to express connexin 43(Cx43) protein intended for establishing electrical coupling between cardiomyocytes and recombinant mammalian cells, wherein the mammalian cells are mesenchymal stem cells. It is reported that the cell may be autologous or allogeneic to the host including human that requires transplantation of genetically modified cell (see col. 14, lines 47-55). Lee et al also teach that Cells may be autologous, allogeneic, or xenogeneic with respect to the host. Thus, teaching of Lee embraces using genetically modified human mesenchymal stem cell to treat a host that is human (see col. 14, lines 56-60, col. 5, line 21, col. 10, line 8).

Regarding claims 49, 57, 59, 66 and 67, Lee et a teach a method of establishing electrical coupling between cardiomyocytes and recombinant mammalian cells which have been genetically engineered to express a connexin 43 (Cx43) protein, wherein the mammalian cells are mesenchymal stem cells (e.g. claims 1 and 2). It is noted that Lee et al teach that "electrical coupling" means the interaction between cells which allows for intracellular communication between cells so as to provide for electrical conduction between the cells in which electrical

excitation of cells through gap junction in the muscle leads to muscle contraction (see col. 10, 20-25). Thus, method of electrical coupling for inducing current is accomplished by injecting MSC to cardiomyocyte in the heart to express the transgene so as to provide for electrical conduction through formation of gap junction meeting the limitation of claims. Regarding claim 51, Lee et al teach a method for treating a cardiac conduction disturbance in a host, the method comprising: introducing into cardiac tissue of said host a therapeutically effective amount of a recombinant mammalian cell genetically modified to express a connexin 43 proteins; wherein the recombinant mammalian cell is a mesenchymal stem cell, and wherein the cell is autologous or allogeneic to the host, wherein said introducing is performed by injection into cardiac tissue of the host, or is performed by cardiovascular infusion into the host, and wherein said introducing is effective to establish an electrical connection between the recombinant cell and a myocardial cell of the host cardiac tissue; and wherein the cardiac conduction disturbance in the host is treated (see claim 8). It is noted that in a preferred embodiment Lee et al report that the host is a human. Further, Lee teaches the methods may also be utilized in combination with other cardiac therapies when appropriate. While Feld, Lee (1) and Lee et al (2) teach all the limitation of the pending claims, but differed from claimed invention by not disclosing MSC comprising nucleic acid encoding HCN2.

The deficiency of Lee is cured by Qu who reported an adenoviral construct comprising nucleic acid encoding HCN2. Qu et al teach treatment of both genetically modified adult and neonatal cells with the AdHCN2 construct resulted in expression of high current levels, with faster activation in neonate (Figures 1B and 1C) (see page 2, col. 2, para. 3). Qu et al suggest that the obvious implications for future efforts would be to alter cardiac rhythm through the regional over expression of selective HCN isoforms. It is suggested that rate can be enhanced by increasing current level, if the expressed current activates at a physiologically relevant threshold voltage in the target tissue (see page 6 (e13), col. 1, para. 3).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition and method disclosed by Feld by substituting the ion channel with one disclosed by Qu. One of ordinary skill in the art would be motivated to use HCN2 as Qu had already shown that HCN2 could be expressed in mammalian cells to induce pacemaker current to alter cardiac rhythm through the regional over expression of HCN isoforms (supra). Furthermore,

one of ordinary skill in the art would be further motivated to substitute the fibroblast cells with MSC to deliver transgene to the heart, with reasonable expectation of successfully forming gap junction with cardiac cells in view of teaching of Lee (2). One of ordinary skill in the art would reasonably conclude that the composition comprising MSCs form gap junction when directly administered to the heart of a subject particularly since Lee taught hMSCs engrafts in the myocardium and forms gap junction with recipient MCS (supra). Therefore, given that MSC including human MSC were available for use to express gene of interest as per the teachings of Lee (1 and II), it would have obvious for one of ordinary skill in the art to use genetically modified MSC as a gene delivery vehicle in the method of Feld. One of skill in the art would have had a reasonable expectation of success in combining the teachings because Feld and Lee et al (2) both had already disclosed establishing electrical coupling between cardiomyocytes and genetically modified mesenchymal stem cells, while Qu provided relevant information about a construct comprising HCN2 for inducing pacemaker current in the heart cells to alter cardiac rhythm. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

***Response to arguments***

To the extent that Applicants' arguments are pertinent to the new rejection of claims, they are addressed as follows:

Applicants' disagree with the rejection and argue that the pending claims should be allowed because the claims should not be considered obvious because there is no teaching or suggestion in either cited reference to include an additional nucleic acid encoding HCN2 in the hMSCs of Lee. Applicant agues that Lee teaches away from including an additional nucleic acid. Applicants assert that Lee, "[p]roduction of connexin in the recombinant cell provides for an electrical connection." Lee focuses on the use of skeletal muscle cells for contractility; Lee teaches that such cells should be transformed with connexins to establish electrical connections with cardiac cells. Applicants further assert that the secondary Qu et al. reference does not cure

the deficiencies of Lee (see page 10 of the argument). Specifically, Qu et al. does not discuss mesenchymal stem cells or their use to deliver genes to the heart or to treat a cardiac rhythm disorder or induce a current in a heart. Applicants argue that to the extent that Lee teaches that the cells can be genetically modified, Lee provides no suggestion that the other genes should encode a protein relevant to pace making (page 11). To the contrary, Lee suggests a gene that encodes N-cadherin, which, like connexin 43 that Lee introduces into cells, is involved in cell-cell connection. Applicants assert that Lee thus actively discourages genetic manipulation of the cells other than to incorporate a connexin thereby teaching away (See page 12). Applicants argue that Qu is strictly concerned with explaining a natural phenomenon and not with any potential clinical uses of HCN2. The mere discussion of HCN2 or its pace making properties should not be considered motivation to use it in Lee's cells (see page 13). Applicants cite several portions of the office action to reiterate that Lee is not concerned with "treating cardiac rhythm disorder" generally, but rather with treating cardiac conditions in which the provision to the heart of additional cells that can become electrically connected to the native cardiomyocytes can alleviate the condition. Since such cells do not provide pacemaker activity, the person of ordinary skill in the art would not have provided motivation. Thus, only impermissible hindsight would have led to the use of an HCN2 transgene in the cells of Lee (see page 14).

Applicants' arguments have been fully considered, but are not found persuasive. Applicants' argument of Lee teaching away from the invention is moot in view of newly applied reference of Feld. As an initial matter applicant should note that claims 51, 57,59, 66 and 67 are broad and recite only one active method step of (i) introducing directly into the human's heart the composition of the inevntion in an amount sufficient to induce pacemaker current expression at the site, (ii) contacting the human cardiomyocyte with the composition of invention in an amount sufficient to induce a pacemaker current in the cardiomyocyte (iii) introducing directly into the human's heart the composition of the invention in an amount sufficient to induce a pacemaker current in the heart or (iv) contacting the human cardiomyocyte with the composition of the invention in an amount sufficient to induce a pacemaker current in the cardiomyocyte. It should be noted that claims 59 and 67 read on an *in vitro* or *in vivo* method of inducing pacemaker current. The composition claims are directed to a composition comprising "a" mesenchymal stem cell (MSC) incorporated with a nucleic acid which encodes a

hyperpolarization activated; cyclic nucleotide gated 2 (HCN2) ion channels, wherein the MSC forms a gap junction with a cell of a mammalian heart. Applicant should note that Feld et al teach a method comprising: (a) providing allogeneic or autogeneic fibroblasts expressing an exogenous voltage-gated or inward-rectifier potassium ion channel polypeptide forming a functional ion channel; and (b) implanting said allogeneic or autogeneic fibroblasts into the heart of the individual by injection, such that each implanted cell of said allogeneic or autogeneic fibroblast forms: (i) gap junctions with at least one cell of the heart; and (ii) a functional ion channel; thereby modifying the electrophysiological function of the heart (supra). Specifically, Feld et al disclose a nucleic acid construct comprising: (a) a first nucleic acid construct including a first polynucleotide region encoding at least one first polypeptide capable of forming a functional ion channel or transporter when expressed within a cell; and (b) a second nucleic acid construct including a second polynucleotide region encoding at least one second polypeptide capable of forming a functional gap junction when expressed within the cell that includes connexin 43 (see col. 4, lines 50-55). Thus, Feld et al clearly teach the claimed active method step, but differ from claimed invention by not explicitly disclosing use of genetically modified MSC as vehicle to deliver transgene and ion channel being HCN2. Lee et al (1) cure the deficiency by providing motivation to use MSC as gene delivery vehicle for treating various conditions, while Lee (2) teach implantation of genetically modified MSC to the heart. In the instant case, it appears that Applicant is arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the level of skill of those in the art is important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Applicants have further engaged in selective reading of the teachings of Lee et al. to formulate the grounds for teaching away.

With respect to applicants' argument that there is no teaching or suggestion in Lee to transfect the cells with a different nucleic acid, it should be noted that such is taught by Feld. To the extent that Feld describes a composition comprising recombinant MSC capable of expressing ion channel and capable of forming gap junction, the rejection is applicable to the instant case

(emphasis added). Qu et al teach HCN ion channel, preferably HCN2 could be expressed in mammalian cells in order to induce pacemaker current in heart. There is no requirement for Qu et al. to teach that which is clearly taught by Feld and Lee et al. It should be noted that prior art recognized that hMSC forms electrical coupling with cardiomyocytes and gene could be delivered to the heart cells or cardiomyocyte, while HCN2 over expression induces pacemaker current in mammalian heart. A person of skill in the art would be motivated to express HCN2 in the recombinant MSC disclosed by Lee, because the method would allow formation of gap junction between recombinant cell and cardiac cell thereby inducing the pacemaker current in the cardiac tissue in the treatment of cardiac rhythm disorder, with a reasonable expectation of success. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

***Conclusion***

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/

Examiner, Art Unit 1632